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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,922	COMINGS, DAVID E.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-59 and 64-73* is/are pending in the application.

4a) Of the above claim(s) *55-59,72 and 73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 29, 2003. Currently, claims 55-59, 64-73 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection necessitated by amendment.

Election/Restrictions

4. Applicant's election with traverse of Group I, Claims 64-67 in the paper filed December 29, 2003 is acknowledged.

Claims 68-73 have been added. Claims 72-73 are drawn to kits which are patentably distinct from the methods of the application. The kits are drawn to products which are classified, for example in 536/23.1. Newly submitted claims 72-73 are directed to an invention that is independent or distinct from the invention originally claimed methods. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 72-73 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The response traverses the restriction requirement stating that the inventions of Group I and III are classified in the same subclassification and therefore no burden exists. This argument has been thoroughly reviewed, but is not found persuasive

because 435/6 is broadly drawn to any nucleic acid assay. A search of all nucleic acids would be a burden. For example, the instant claims each claim different method steps and have different goals. A search of Claim 55 is not coextensive of a search of claim 64. Therefore a burden would exist to search Group I and III together.

The response argues that Claim 55 is drawn to a novel method for reliably determining whether particular candidate genes contribute to ADHD, a polygenic disorder. The response asserts that "once genes have been predetermined by this method to contribute, a subject can be tested for non-wild type alleles of each gene in the panel." This argument has been thoroughly reviewed, but is not found persuasive because Claim 64 is directed to using the predetermined genes of Claim 55, but not using the method of Claim 55.

Moreover, the response asserts that newly added Claim 68-73 are directed to determining whether a subject is at risk for ADHD. There is no dependency on Claim 55, thus, the response's arguments that these claims are to be grouped with Claim 64-67 further supports that the claims do not require performing the method of Claim 55 prior to each method of determining whether a subject is at risk for ADHD.

Claims 64-71 will be examined on the merits. Claims 55-59, 72-73 have been withdrawn from consideration.

Priority

5. This application claims priority to provisional application 60/195,312, filed April 10, 2000.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 64-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of determining a risk of an individual for attention deficit hyperactivity disorder (ADHD) by determining whether a subject has a non-wild-type allele from at least one gene selected from TPH, PNMT, ADOA2A, NOS3 and NAT1 and to methods of determining for each of the genes a wild-type or non-wild type allele.

The specification teaches analyzing numerous genes for their association with ADHD. Figure 1 illustrates the ANOVA of ADHD scores for 40 genes. Figure 1A-2 teaches TPH SNP A779C has a p values of 0.495. Figure 1A-3 teaches PNMT GNP G-148A has a p value of 0.129. Figure 1B-2 teaches ADORA2A C108T (RsaI) has a p-value of 0.229. Figure 1B-2 teaches NOS3 has a p value of 0.830. Finally, Figure 1B-3 teaches NAT1 T1088 have a p value of 0.329. It is noted that none of these p-values are significant at alpha= 0.05. Figure 2 appears to illustrate 22 genes when combined are associated with ADHD, however, it is unclear which 22 genes are involved in the analysis. Figure 3 appears to illustrate that each of TPH, PNMT, ADOA2A, NOS3 and NAT1 have a p values <= 0.05 for ADHD. Thus, there is apparent confusion between Figure 3 and Figure 1. The specification teaches there were 326 unrelated, non-Hispanic Caucasians. 271 of the subjects have Tourette syndrome and 55 were controls (page 9, lines 20-25). The text of the specification teaches ADOA2A was significant at $p < 0.05$ (page 12, lines 15-18). Moreover, the specification teaches that "the only other new gene that produced a significant individual result was the NAT1 gene" (page 13, lines 10-11). With respect to NOS3, the specification teaches that NOS3 was significantly involved with all three traits" (page 15, lines 54-28).

The art teaches analysis of numerous genes in ADHD including ADOA2A, NAT1 and NOS3. Comings (Clin. Genet. Vol. 58, pages 31-40, July 2000) teaches each of these genes are not significantly associated with ADHD (Table 1). With respect to TPH, the art teaches there is a lack of association between the A218C polymorphism and ADHD in Chinese Han population. Tang (Am. J. of Med. Genetics, Vol. 105, pages 485-488, August 2001) teaches that the negative results of the study may be limited to the Chinese Han population or that the A218C polymorphism is not functionally significant and that some other variants are associated with ADHD (page 487, col 1-2).

The art also teaches that ADRA2A and ADRA2C genotypes are individually associated with ADHD (Comings et al. Clin. Genet. Vol. 55, pages 160-172, 1999, Table 2, page 165).

Comings et al. (AM. J. of Medical Genetics, Vol. 67, pages 264-288, 1996) teaches analyzing the additive effect of genes for ADHD. As seen in Figure 2, the listing of all possible combinations of the three markers is illustrated. The most densely shaded area shows the part of the ADHD score that is diagnostic for ADHD. It is clear from figure 2 that each of the genes individually is not diagnostic of ADHD. It is only the combination of all three and the combinations of at least two. Therefore, the skilled artisan is clearly not enabled to detect ADHD using a single gene, as claimed by the instant claims.

Moreover, Blum (US Pat. 6,132,724, October 2000) teaches association of CHRNA4 gene with ADHD (Example 28, col. 306). Similarly, Blum teaches the additive

effect of three adrenergic genes (ADRA2A, ADRA2C, DBH) on ADHD subjects (Example 27, col. 294).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. Based upon the teachings in the specification, it is unclear how to interpret the data. For example, the figures appear to illustrate that the genes are both significant and not significant. Therefore, it is unclear what is being shown in the figures and whether the genes are significant alone, i.e. not in combination with other genes. Moreover, it is unclear whether each of the combinations of gene are significantly associated with ADHD, or whether only the combination of 22 genes is significantly associated with ADHD.

Additionally, the claims are drawn to detecting a non-wild-type allele in the recited genes. The specification and the art have taught either a single SNP per gene or a couple of SNPs. The specification has not described which non-wild-type alleles are associated with ADHD and which alleles are neutral polymorphism. Numerous SNPs in the genome are known to be unassociated with diseases, especially with ADHD in particular. Therefore, the mere detection of a non-wild-type allele within TPH, PNMT, ADOA2A, NOS3 or NAT1 does provide indication that the subject is at an increased risk for ADHD. The specification has examined SNP A779C within TPH gene; SNP G-148A within PNMT; SNP C108T (RsaI) within ADOA2A; and T1088A within NAT1. These specific mutations are not representative of all non-wild-type alleles within the genes. In order to practice the invention as broadly as claimed the skilled artisan would be required, unduly, to analyze the recited genes for alleles, determine

whether they are wild-type or non-wild-type alleles and analyze the alleles for an association with ADHD. This trial and error experimentation is unpredictable. It is unpredictable whether the gene has alleles aside from the alleles studied in the instant application, whether these alleles are associated with ADHD, and whether the alleles confer an increased risk for ADHD or whether the alleles are protective and in fact are indicative of a decreased risk for ADHD. Moreover, the skilled artisan would be required to analyze numerous populations which are representative to determine whether the allele is associated with an increased risk over populations in general or whether the allele is associated within only certain populations. For example, in the instant case, in the event that the TPH gene A218C polymorphism is associated with non-Hispanic Caucasians, as asserted in the specification, the art teaches that there is no association in Chinese Han populations. Moreover, the specification teaches that there are differences in associations between various ethnic or racial backgrounds (page 7). The specification has only sampled unrelated non-Hispanic Caucasians. The specification has not provided a broad based population study which would be representative of numerous populations.

Furthermore, with respect to the particular combination of genes, the specification fails to provide any evidence that this subsection of the 22 genes which were analyzed provides any association with ADHD. As discussed above, detecting any non-wild type allele would not be necessarily indicative of ADHD, as all SNPs and alleles within genes are not all correlated with disease state. Without an indication that

there five alleles provide significant association with ADHD, it is unpredictable that the skilled artisan could use these five alleles for detecting ADHD.

Therefore, based upon the analysis above, neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 64-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 64-67 are directed to a method for determining whether a subject is at risk for ADHD using a prederemined gene. Claim 65, which depends on Claim 64 is directed to particular non-wild type alleles. Since Claim 65 depends from Claim 64, the genes within 65 must have been predeteremined by the method of 55, as required by Claim 64. Therefore, once the genes have been predetermined, the method only requires a method for determining whether a subject is at risk for ADHD by determining if the subject has a non-wild type allele, for example determining whether a subject has TPH SNP A779C wherein the presence of the non-wild type allele indicates the subject is at risk for ADHD. Alternatively, the claim could be construed to perform all of the method step of Claim 55 each time prior to determining whether a subject is at risk for ADHD. For example, in determining whether patient A is at risk for ADHD, a group of

ADHD patients is identified, a group of genes is selected, polymorphisms are identified, a scale is created, a gene score is assigned to each gene, additive variance is determine, and statistical significance is calculated, then determining whether the patient has one of these non-wild type alleles to assess risk for ADHD. The same method would be required for patient B, C, D etc despite the fact that the information had already been gained by predetermining the association of the genes. The method, as written, must be read in one of these two ways. Since the second alternative seems uncommon in the scientific world, the examiner has presumed that the first method of using predetermined genes is intended. In the event that applicant wishes the claim to be directed to the second alternative, the applicant is requested to clearly write the claim to include all of the steps of Claim 55 as affirmative process steps.

B) Claim 68-71 are directed to methods of determining whether a subject is at risk for ADHD by determining for EACH of 5 genes whether the subject comprises a wild type or non-wild type allele of the gene as indicative of ADHD. Claim 69 is directed to "said at least one non-wild type allele.." The phrase lacks proper antecedent basis. Claim 68 fails to refer to at least one non-wild type allele.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 64-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Blum (US Pat. 6,132,724, October 2000).

Blum teaches a method for determining the additive and subtractive effect of all 29 gene son the ADHD score (see Figure 5, col. 32, lines 55-68). Blum teaches that by examining the additive effect of multiple genes rather than examining genes one gene at a time, the MAA technique has much more power to identify the genes involved in polygenic disorders than procedures such as lod score, sib pair, haplotype relative risk and transmission disequilibrium tests (col. 36, lines 45-50). Blum teaches identifying a polygenic disorder or train to be studied i.e. ADHD (col. 36); setting a scale that measures the severity of the polygenic disorder (col. 37); identifying candidate genes to be tested (col. 37); identifying one or more polymorphisms associated with each gene (col. 46); assigning a score to the genotypes based on independent studies showing which genotypes are associated with the highest quantitative scores and which are associated with the lowest scores (col. 58); setting up a dummy polygenic variable (col. 59); performing regression analysis of PG versus QT or DV (col. 59); plotting the results (col. 60). Figure 5 shows the additive and subtractive effect for genes for ADHD. Figure 6 illustrates the additive genes (col. 60). In example 27, Blum teaches the

additive effect of three adrenergic genes (ADRA1A, ADRA2C and DBH) on ADHD (col. 294). Blum teaches that there are two potential approaches to use for the regression analyses: univariate and multivariate (col. 188, lines 50-52).

9. Claim 64 is rejected under 35 U.S.C. 102(b) as being anticipated by Comings et al. (AM. J. of Medical Genetics, Vol. 67, pages 264-288, 1996).

Comings et al. (herein referred to as Comings-1) teaches analyzing individuals for risk of ADHD using polymorphisms of three different dopaminergic genes. Comings-1 teaches analyzing subjects which are patients at the TS clinic (page 269, col. 1). The dopaminergic genes were studied. DRD2 polymorphism, DBH and DAT1 polymorphisms were analyzed. A scale was created for ADHD variables (page 269). Statistics were performed using ANOVA analysis, multiple linear regression and R2 values were determined for all three of the genes. Comings-1 teaches that this provides the total proportion of the variance accounted for by all three genes together, for each specific behavior (page 270, col. 2). Comings-1 teaches that "in polygenic disorders, the critical variable is the number of mutant genes present, rather than the consistent presence of a given mutant gene in affected members and its absence in unaffected members" (page 276c, col. 1). As seen in Figure 2, the listing of all possible combinations of the three markers is illustrated. The most densely shaded area shows the part of the ADHD score that is diagnostic for ADHD. It is clear from figure 2 that each of the genes individually is not diagnostic of ADHD. It is only the combination of all three and the combinations of at least two.

10. Claims 64-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Comings et al. (Clin. Genet. Vol. 55, pages 160-172, March 1999).

Comings et al. (herein referred to as Comings-2) teaches the additive effect of three noradrenergic genes on ADHD. Comings-2 teaches sampling subjects, genotyping ADRA2A, ADRA2C, DBH, DRD2, DAT1, DRD5 (pages 163-164); clarifying severity of ADHD (page 164, col. 1); assigning a gene score to the genotypes (page 164, col. 1); and statistically analyzing using regression to determine the additive effect on the genes. Commings teaches sampling ADRA2A and ADRA2C (page 163, col. 2)(limitations of Claim 65). As seen in Figure 2, the additive effect of the genes on ADHD is provided. The p values are more significant with only two genes. Comings teaches that looking at additive scores also has the advantage that if a gene happens not to play a role in a given subject, or group of subjects, but a a different gene with a similar function is present, the effect of both can be included (page 168, col. 2). Comings teaches figures which illustrate that more variance is accounted for, the greater the number of genes. "While these figures may seem small, as more and more genes are added, the percentage of the variance accounted for continues to rise" (limitations of Claims 66-67).

11. Claims 64-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Comings et al. (Clin. Genet. Vol. 57, pages 178-196, March 2000).

Comings teaches a comparison of the role of dopamine, serotonin and noradrenaline genes in ADHD using multivariate regression analysis of 20 genes.

Comings teaches scoring of genes to determine r2 values using linear regression analysis (page 179, col. 2). Comings teaches that multivariate linear regression analysis with backward elimination was used to examine a composite effect of multiple genes. The genes include dopamine genes, serotonin gene and noradrenergic genes (page 180, col. 2). Non-Hispanic, Caucasian subjects were sampled (page 181). Polymorphisms from each of the genes was analyzed by genotyping. Gene scores were assigned and statistics were performed. Multivariate linear regression analysis with backward elimination was used to examine the correlation between the gene scores and the ADHD score, using the ADHD score as the dependent variable, with the gene scores as the independent variables.

Conclusion

12. No claims allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571)272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
February 18, 2004